Dynamics of Weight Change After Initiation of Contemporaneous Antiretroviral Therapy in Treatment-Naive HIV-1 Infected Patients: Results From the Belgian HIV Cohort 2015–2021

To the Editors:

INTRODUCTION

Weight gain has emerged as a novel side effect of contemporaneous antiretroviral therapy (ART) in people living with HIV (PLWH). Although it can be considered as a return to normal weight effect among ART-naive patients with low CD4 count, the extent of weight change is influenced by the composition of the initiated ART regimen.[1,2] Both clinical trials and observational studies have documented associations of weight change after ART initiation with the use of integrase strand transfer inhibitors (INSTIs) and tenofovir alafenamide (TAF). Most data are available for the INSTIs dolutegravir (DTG), elvitegravir (EVG), and raltegravir (RAL), whereas weight change after bictegravir (BIC) initiation has been less well assessed in real-life setting. The effect of INSTIs on weight seems to be heterogeneous in nature and is more prevalent among women and patients of Black ethnicity.[3] Furthermore, most of the weight gain occurs in the first 2 years after ART initiation,[2] but the kinetics of weight gain have not been compared between different first-line single-tablet regimens. We therefore aimed to model the change in weight and body mass index (BMI) in a large consecutive group of treatment-naive adults with HIV after initiation of 3 contemporaneous first-line treatment options, including TAF/emtricitabine (FTC)/BIC.

METHODS

Study Population and Data Collection

The population of interest were treatment-naïve adults with HIV in care in 10 Belgian HIV Reference Centers (HRC). Patients were eligible to be included if they were newly diagnosed with HIV-1 by a Belgian Aids Reference Laboratory (ARL) between January 1, 2015, and December 31, 2021, and started first-line ART maximally 1 year after the date of diagnosis (n = 1684). Reasons for exclusion were pregnancy (n = 40), not being prescribed a single-tablet regimen (n = 489), and less than 2 weight measurements available during the first 18 months of first-line ART (n = 182). Finally, we excluded 245 patients who were on a single-tablet regimen taken by less than 100 patients (see Figure 1, Supplemental Digital Content, http://links.lww.com/QAI/C27). The design and characteristics of the Belgian HIV cohort have been previously described[4]: individual-level data from PLWH in Belgium were collected through standardized data registries and managed by Sciensano, the Belgian Institute of Health. Sciensano is legally entitled to collect these data for HIV surveillance, approved by an independent administrative authority protecting privacy and personal data.[5] This study was approved by the Ethical committee of AZ Sint Jan Brugge Oostende AV (advice number 2973).

Statistical Analyses

The outcomes of interest were the changes in weight and BMI over the course of the first 18 months after initiation of first-line ART. Follow-up ended if the patient was switched to a second-line ART before 18 months, ART was stopped, or the patient deceased.[6] The following variables were included in the model as baseline covariates: age, sex, place of residence, nationality, ethnicity, height, probable mode of transmission, the presence of acute HIV infection at diagnosis, smoking, systolic blood pressure, CD4 count, plasma viral load, and the presence of an AIDS-defining illness/cancer at baseline. We considered the median taxable income of the patient's municipality as a proxy of his socioeconomic status because the individual taxable income was not available. All statistical analyses were performed in R 4.1.2 (R Core Team, 2021). Twenty-fold multilevel multiple imputation was performed to account for missing data.[7] Multivariable linear mixed models were used to describe the kinetics of weight and BMI changes.[6,8,9] Models were fitted on each imputed data set and pooled using the Rubin rule. A first sensitivity analysis was conducted where patients were excluded if they had an extreme high or low baseline weight/BMI (cutoff on 2.5 and 97.5 percentiles). A second sensitivity analysis was performed using plasma viral load as a time-varying covariate to control for potential differential adherence to the ART regimen. More details on statistical modeling can be found in Supplementary materials.

RESULTS

A total of 728 treatment-naive adults with HIV-1 were included in the analysis: 407 patients were prescribed FTC/TAF/BIC, 201 patients DTG/lamivudine(3TC)/abacavir (ABC), and 120 patients FTC/TAF/cobicistat-elvitegravir(cEVG). The overall and ART-specific patient characteristics and observed weight and BMI data are summarized in Table 1 and presented in Figure 2, Supplemental Digital Content, http://links.lww.com/QAI/C27.

Adjusted mean weight and BMI trajectories are shown in Figure 1, and slopes and contrasts between them are summarized in Table 2, Supplemental Digital Content, http://links.lww.com/QAI/C27. We used a piecewise linear change

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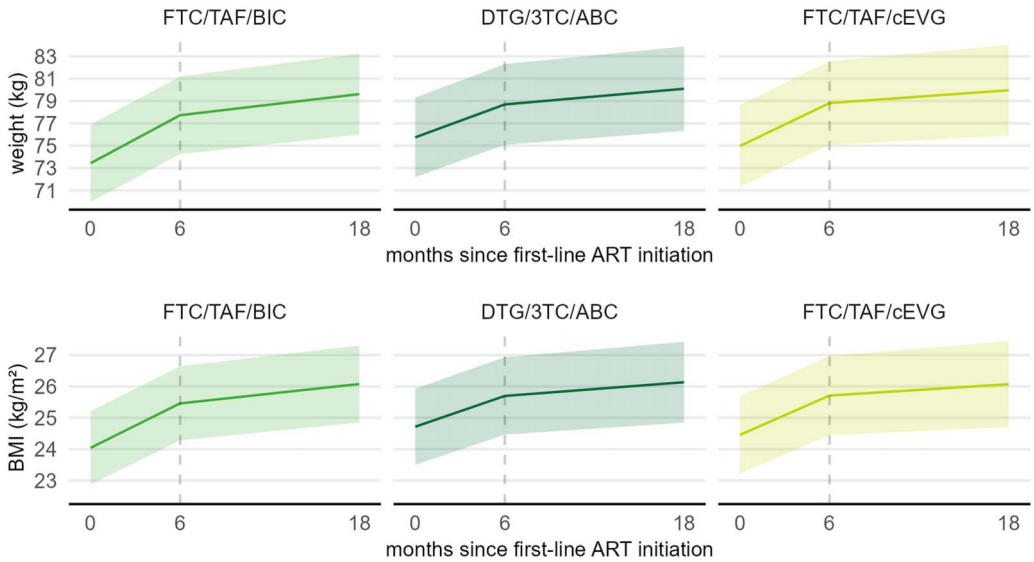

FIGURE 1. Adjusted weight (top) and BMI (bottom) changes in treatment-naïve adults with HIV-1 from baseline to 18 months after initiation of first-line ART. The trajectories represent the average with 95% CI for a "reference" subject (heterosexual White Belgian male, aged 40 years, 175 cm in height, diagnosed in 2018, systolic blood pressure of 120 mm Hg, nonsmoker, living in a municipality with median taxable income of €25.000, diagnosed without acute HIV infection, baseline CD4 count <200/μL, baseline viral load >10.000/mL, and no AIDS-related cancer or illness at baseline). 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; BIC, bictegravir; BMI, body mass index; cEVG, cobicistat/elvitegravir; DTG, dolutegravir; FTC, emtricitabine; TAF, tenofovir alafenamide.

over time with a knot at 6 months after ART initiation. The slopes for all 3 ART regimens were positive in each period but decreased after 6 months. The slopes of weight and BMI gain were highest in FTC/TAF/BIC in each period, but a significant difference was observed only for DTG/3TC/ABC in the first 6 months (for weight gain, 0.72 kg/month (95% CI: 0.61 to 0.82) versus 0.49 kg per month (95% CI: 0.34 to 0.64)). No significant differences in weight or BMI gain between FTC/TAF/BIC and FTC/TAF/cEVG were found before and after 6 months of treatment. For FTC/TAF/cEVG, the increase in weight and BMI observed after 6 months was statistically nonsignificant.

Figure 3, Supplemental Digital Content, http://links.lww.com/QAI/C27 shows the associations of weight and BMI with the covariates that were controlled for in both models. Except for height, all associations had the same direction with weight and BMI. Older age and higher systolic blood pressure were associated with a higher average weight and BMI, and an AIDS-defining illness or cancer was associated with a lower average weight and BMI. Other covariates of interest had no significant association with weight or BMI.

Exclusion of patients with an extremely high or low baseline weight/BMI did not substantially affect the contrasts between the slopes of weight/BMI gain (see Table 3, Supplemental Digital Content, http://links.lww.com/QAI/C27). Inclusion of VL as a time-varying covariate instead of the baseline value also had no substantial effect on the contrasts between slopes (see Table 4, Supplemental Digital Content, http://links.lww.com/QAI/C27).

DISCUSSION

In this multicenter observational cohort study, we modeled the change in weight and BMI during the first 18 months after ART initiation in 728 treatment-naïve patients with HIV-1, comparing 3 contemporaneous single-tablet regimes. The increase in weight and BMI, after adjustment for several covariates, was highest in the first 6 months and decreased thereafter for all regimens. FTC/TAF/BIC was associated with significantly higher gains in the first 6 months compared with DTG/3TC/ABC but not with FTC/TAF/cEVG. In the following 12 months, weight and BMI were significantly raising further in the FTC/TAF/BIC group and to a lesser extent in the DTG/3TC/ABC group, whereas there was no statistically significant weight gain in the FTC/TAF/cEVG group. These observational findings suggest that the trajectories of weight and BMI after ART initiation are dependent on the composition of the treatment and underline the importance of counseling patients for anticipated weight change after ART initiation.[10]

This large observational study is the first to compare short-term weight and BMI changes after ART initiation between a TAF- and BIC-containing regimen, a DTG-based regimen, and a TAF- and cEVG-containing regimen. A previous observational study found that adult PLWH starting a DTG-based regimen gained significantly more weight at 18 months compared with those starting a cEVG-based regimen. However, TDF/FTC was used then as backbone.[9]

Limitations of this study include the exclusion of patients whose weight data were not available and absence of correction for other potential confounding factors including comorbidities, non-ART medication, diet, and exercise. Finally, well-designed randomized trials are needed to confirm our findings.

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Risk of Cardiovascular Diseases or Mortality in People With Higher Values of HIV-1 DNA

To the Editors:

Total HIV-1 DNA is the most widely used marker for quantifying HIV reservoir,[1,2] capable to estimate all forms of HIV-1 DNA in the infected cells but not to differentiate the replication-competent virus. Compared with the quantitative viral outgrowth assay that is currently considered the gold standard for measuring latent HIV-1 burden, total HIV-1 DNA is both easier to perform and more cost-effective, although it can lead to an overestimation of viral reservoir.[3–5]

Recent studies have demonstrated the relevance of quantifying total HIV-1 DNA load during HIV infection as a predictive marker of disease progression in people living with HIV (PLWH).[6,7]

The aim of our study was to evaluate if total HIV-1 DNA may be associated with clinical outcomes, specifically the occurrence of cardiovascular (CV) events or mortality.

We conducted a retrospective study on adult PLWH followed at IRCCS San Raffaele Hospital, Milan, Italy, with at least 10 years of exposure to antiretroviral therapy (ART) and 5 years of follow-up from the first total HIV-1 DNA determination (baseline).

We considered all the major adverse cardiac events (myocardial infarction, unstable angina, coronary or peripheral arterial revascularization, heart failure, stroke or transient ischemic attack, peripheral arterial ischemia, cardiac arrest) and deaths from any causes as clinical outcomes.

Total HIV-1 DNA was quantified in peripheral blood mononuclear cells (PBMCs) by real-time PCR (ABI Prism 7900). Patients' characteristics were reported as median (interquartile range) or frequency (%). Baseline characteristics in PLWH with HIV-1 DNA $\geq$100 copies/10^6 PBMCs and HIV-1 DNA $<$100 copies/10^6 PBMCs were compared using the χ^2/Fisher exact test or the Wilcoxon rank sum test. Both survival and CV events probabilities were estimated by Kaplan–Meier (KM) curves and compared by the log-rank test. PLWH with at least a CV event occurred before the first HIV-1 DNA determination were excluded from the analyses.

Multivariable Cox proportional hazard model was applied to assess risk factors for CV events or mortality (composite endpoint); adjusted hazard ratio (aHR) with the respective 95% confidence intervals (95% CIs) were estimated. Time-dependent variables (CD^{4+} T-cell count, HIV-1 RNA, age, and years of ART exposure) together with sex and HIV-1 DNA $\geq$100 copies/

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